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The application was originally filed in English.

(71) *Sökande* *AstraZeneca AB, Södertälje SE*
Applicant (s)

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PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

NOVEL COMPOUNDS

Field of the Invention

This invention relates to novel 2-heteroaryl- and 2-aryl- 7-azaindole [2-(hetero)aryl-1H-pyrrolo[2,3-b]pyridine] derivatives, processes for their preparation, intermediates thereto, pharmaceutical compositions comprising them, and their use in therapy.

Background of the Invention

Inducible T cell Kinase (Itk) is a member of the Tec-family of cytosolic protein tyrosine kinases. In mammalians, this family also includes Btk, Tec, Bmx, and Txk. These kinases regulate various immune cell functions that integrate signals given by the other cytosolic tyrosine kinases as well as serine/threonine kinases, lipid kinases, and small G proteins. Tec-family kinases have the following general structure: a N-terminal pleckstrin-homology (PH) domain, a Tec-homology domain that includes a Btk motif and one or two proline-rich (PR) motifs, a SH3 domain, a SH2 domain and a c-terminal catalytic (SH1) domain. These kinases are expressed exclusively in hematopoietic tissues, with the exception of Tec and Bmx that have also been detected in endothelial cells. The cellular distribution is different for the Tec-family members. For example, Itk is expressed by T cells, NK cells and mast cells, whereas Btk is expressed by all hematopoietic cells except T cells. Thus, hematopoietic cells may express one or several Tec-family kinases. For example, T cells express Itk, Tec and Txk, and mast cells express Btk, Itk and Tec.

Btk is by far the most extensively studied among the Tec-family kinases, due to its association with X-linked agammaglobulinemia (XLA), and Btk is currently the only Tec-family kinase with a known human phenotype. XLA patients are virtually devoid of mature B cells and their Ig levels are strongly reduced.

$Itk^{-/-}$ mice show defects in T cell activation and differentiation. T helper 2 (Th2) differentiation is disrupted in these mice, whereas Th1 differentiation is apparently intact.

In T and B cells, signalling through T cell receptors and B cell receptors leads to activation of Itk and Btk, respectively. Downstream of Itk and Btk a number of different messengers

are engaged; scaffolding proteins (SLP-76, LAT, SLP-65), Src kinases, MAP kinases, and PI3-K. These events are followed by PLC-γ activation that leads to IP3 generation and sustained Ca^{2+} flux, and subsequently activation of transcription factors. PLC-γ1 has been suggested as a direct substrate for Itk.

In T cells, Itk (and Tec) may also mediate signalling through the CD28 co-receptor. Furthermore, Itk has in T cells been implicated in the activation of β-integrin. Signalling from Tec-family kinases can also be regulated by PH domain-mediated plasma membrane localization, and by Src-family-mediated phosphorylation of critical tyrosine residues. Interestingly, Itk, Btk and Txk have recently been shown to translocate to the nucleus after activation.

From studies using Itk-/- mice, it has been proposed that Itk is required for Th2 but not Th1 cell development. This was demonstrated in the *N. brasiliensis* and *L. major* infection models where the Itk-/- animals are protected in the Leishmania model indicating an intact Th1 response, whereas they are susceptible to infection with *N. Brasiliensis* that requires an intact Th2 response for resolution of the infection. This indicates that modulation of Itk activity may prove useful for treatment of Th2-driven disorders and conditions.

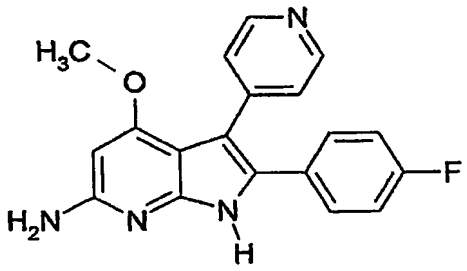
We have identified the critical role of Itk in regulating important mast cell and basophil functions and established that the activity of mast cells or basophils may be inhibited through inhibition of Itk. Thus Itk inhibitors may be used as pharmaceutical agents for the treatment of mast cell-driven or basophil-driven conditions or diseases. In particular, we have identified Itk as a target for inhibiting several key events in both acute and late phase allergic reactions common to allergic rhinitis and asthma.

WO 98/47899 discloses certain 6-substituted 3-(4-pyridyl)-1H-pyrrolo[2,3-b]pyridines and 6-substituted 3-(4-pyrimidyl)-1H-pyrrolo[2,3-b]pyridines as inhibitors of p38 kinase. The compounds are useful in the treatment of diseases associated with the overproduction of inflammatory cytokines. Certain compounds disclosed in this application are disclaimed from the scope of the present invention.

WO 99/20624 discloses certain aza- and diaza- indoles as inhibitors of p38 kinase. However, 7-azaindoles in which N-1 is unsubstituted are not disclosed in this application.

WO 01/47922 discloses substituted aza- and diaza- indoles as kinase inhibitors, in particular, as inhibitors of the protein tryosine kinase Syk.

Henry, J. R. et al., J. Med. Chem. 41 (1998) 4196 describe certain 6-amino-2-(4-fluorophenyl)-3-(4-pyridyl)-1H-pyrrolo[2,3-b]pyridines such as the compound:



as p38 kinase inhibitors.

The compounds disclosed in J. Med. Chem. 41 (1998) 4196 and in WO 01/47922 are not within the generic scope of the present application.

Henry, J. R. et al., Bioorg. Med. Chem. Letters, 1998, 8, 3335-3340 discloses the compound 2-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrrolo[2,3-b]pyridine as a p38 kinase inhibitor.

Patent application JP 11-305996 discloses, *inter alia*, certain 3-(4-hydroxyphenyl)- and 3-(4-hydroxy-3-pyridyl)- azaindole derivatives. The compounds have activity at the oestrogen receptor and are thereby useful in the treatment of osteoporosis. Certain

compounds disclosed in this patent application are disclaimed from the scope of the present invention.

JCS Perkin I, 1980, 506-511 discloses the compound 2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine.

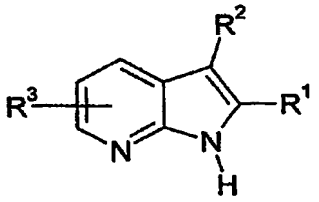
J. Chem. Soc. (C) 1969, 1505-1514 discloses the compound 4-methyl-2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine.

None of the above publications are concerned with compounds that have utility as inhibitors of the kinase Itk.

The present invention discloses novel substituted 2-heteroaryl- and 2-aryl- 7-azaindoles that have activity as Itk inhibitors and are thereby useful as pharmaceuticals, particularly for the treatment of allergic rhinitis and of asthma.

Disclosure of the Invention

The present invention provides a compound of formula (I):



(I)

wherein:

R^1 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms selected independently from O, S and N; said phenyl or aromatic heterocyclic

ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy or CO_2R^4;

R^2 represents a saturated or partially unsaturated 4 to 7 membered ring, optionally including 1 or 2 heteroatoms independently selected from O, N and $S(O)_n$ and optionally incorporating 1 or 2 carbonyl groups; and optionally substituted by halogen, OH, C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkanoyl, C1 to 4 alkylsulphonyl or CO_2R^5;

or R^2 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CN, CO_2R^6 and a group –W-X-Y;

W represents O or a bond;

X represents C1 to 4 alkyl, -CO-, $-CH_2CHOHCH_2-$ or a bond;

Y represents NR^7R^8;

or Y represents a saturated or partially unsaturated 4 to 7 membered ring, optionally including 1 or 2 heteroatoms independently selected from O, N and $S(O)_n$ and optionally incorporating 1 or 2 carbonyl groups; and optionally substituted by one or more substituents selected independently from OH, C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkanoyl, C1 to 4 alkylsulphonyl or CO_2R^5;

or Y represents C1 to 4 alkoxy optionally further substituted by OH or C1 to 4 alkoxy;

R^3 represents H, halogen, C1 to 4 alkyl, C1 to 4 alkoxy or cyano;

R^4, R^5 and R^6 independently represent H or C1 to 4 alkyl;

R^7 and R^8 independently represent H, C1 to 4 alkyl, $-CH_2CHOHCH_2OH$, C1 to 4 alkanoyl or a group –G–J–K wherein G represents –CO– or a bond; J represents C1 to 4 alkyl; and K represents $-NR^9R^{10}$ or $-CH(NH_2)CO_2R^{11}$;

R^9 and R^{10} independently represent H or C1 to 4 alkyl; or the group $-NR^9R^{10}$ together represents a saturated 5 or 6 membered azacyclic ring;

R^{11} represents H or C1 to 4 alkyl;

n represents an integer 0, 1 or 2;

and pharmaceutically acceptable salts thereof;
provided that:
(i) when R^3 is at the 6-position and represents C1 to 4 alkoxy and at the same time R^1 represents optionally substituted phenyl, then R^2 does not represent unsubstituted 4-pyridyl or unsubstituted 4-pyrimidyl; and
(ii) when R^2 represents 4-hydroxyphenyl or 4-hydroxy-3-pyridyl either optionally further substituted by halogen, C1 to 4 alkyl or C1 to 4 alkoxy, then R^3 represents cyano; and
(iii) the following three compounds are disclaimed - 2-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrrolo[2,3-b]pyridine; 2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine; and 4-methyl-2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine.

The compounds of formula (I) may exist in enantiomeric forms. All enantiomers, diastereoisomers, racemates and mixtures thereof are included within the scope of the invention.

Compounds of formula (I) may also exist in various tautomeric forms. All possible tautomeric forms and mixtures thereof are included within the scope of the invention.

Unless otherwise indicated, the term "C1 to 4 alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 4 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

Unless otherwise indicated, the term "C1 to 4 alkoxy " referred to herein denotes an oxygen substituent bonded to a straight or branched chain alkyl group having from 1 to 4 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy and s-butoxy.

Unless otherwise indicated, the term "C1 to 4 alkanoyl" referred to herein denotes a carbonyl group attached to a straight or branched chain alkyl group having from 1 to 3 carbon atoms. Examples of such groups include formyl, acetyl and propionyl.

Unless otherwise indicated, the term "C1 to 4 alkylsulphonyl" referred to herein denotes a sulphonyl group, $-SO_2-$, attached to a straight or branched chain alkyl group having from 1 to 4 carbon atoms. Examples of such groups include methylsulphonyl and ethylsulphonyl.

Unless otherwise indicated, the term "halogen" referred to herein denotes fluorine, chlorine, bromine and iodine.

Examples of a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected independently from O, S and N include furan, thiophene, pyrrole, pyridine, imidazole, thiazole, oxazole, isoxazole, isothiazole, triazole, oxadiazole, pyrazine and pyrimidine.

Examples of a saturated or partially unsaturated 4 to 7 membered ring, optionally including 1 or 2 heteroatoms independently selected from O, N and $S(O)_n$ and optionally

incorporating 1 or 2 carbonyl groups include cyclopentane, cyclohexane, cycloheptane, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, pyrrolidinone, oxazolidinone, piperidinone, tetrahydrofuran, cyclopentene, dihydroimidazole and dehydropiperidine.

Examples of a saturated 5 or 6 membered azacyclic ring include pyrrolidine and piperidine.

In one embodiment, R^1 in formula (I) represents optionally substituted phenyl, furyl, thienyl, thiazolyl, pyrrolyl or oxazolyl. In another embodiment, R^1 represents phenyl, furyl or pyrrolyl, optionally substituted by C1 to 2 alkoxy or halogen.

In one embodiment, R^3 in formula (I) is at the 5-position of the azaindole ring system. In one embodiment, R^3 represents halogen or cyano. In another embodiment, R^3 represents bromo or cyano

In one embodiment, R^2 in formula (I) represents a saturated or partially unsaturated 4 to 7 membered ring, optionally including 1 or 2 heteroatoms independently selected from O, N and $S(O)_n$ and optionally incorporating 1 or 2 carbonyl groups; and optionally substituted by halogen, OH, C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkanoyl, C1 to 4 alkylsulphonyl or CO_2R^5;

In one embodiment, R^2 represents optionally substituted piperazine.

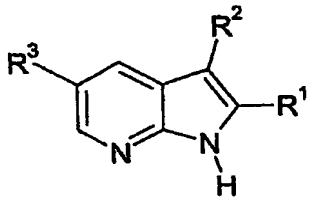
In another embodiment, R^2 in formula (I) represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CN, CO_2R^6 and a group –W-X-Y;

In another embodiment, R^2 represents phenyl substituted by C1 to 4 alkoxy or by a group

–W–X–Y.

In another embodiment W in formula (I) represents O.

In one embodiment, the invention provides a compound of formula (Ia)



(Ia)

wherein:

R^1 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms selected independently from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy or CO_2R^4;

R^2 represents a saturated or partially unsaturated 4 to 7 membered ring, optionally including 1 or 2 heteroatoms independently selected from O, N and $S(O)_n$ and optionally incorporating 1 or 2 carbonyl groups; and optionally substituted by halogen, OH, C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkanoyl, C1 to 4 alkylsulphonyl or CO_2R^5;

or R^2 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CN, CO_2R^6 and a group –W-X-Y;

W represents O or a bond;

X represents C1 to 4 alkyl, -CO-, $-CH_2CHOHCH_2-$ or a bond;

Y represents NR^7R^8;

or Y represents a saturated or partially unsaturated 4 to 7 membered ring, optionally including 1 or 2 heteroatoms independently selected from O, N and $S(O)_n$ and optionally incorporating 1 or 2 carbonyl groups; and optionally substituted by one or more substituents selected independently from OH, C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkanoyl, C1 to 4 alkylsulphonyl or CO_2R^5;

or Y represents C1 to 4 alkoxy optionally further substituted by OH or C1 to 4 alkoxy;

R^3 represents halogen, C1 to 4 alkyl, C1 to 4 alkoxy or cyano;

R^4, R^5 and R^6 independently represent H or C1 to 4 alkyl;

R^7 and R^8 independently represent H, C1 to 4 alkyl, $-CH_2CHOHCH_2OH$, C1 to 4 alkanoyl or a group –G–J–K wherein G represents –CO– or a bond; J represents C1 to 4 alkyl; and K represents $-NR^9R^{10}$ or $-CH(NH_2)CO_2R^{11}$;

R^9 and R^{10} independently represent H or C1 to 4 alkyl; or the group $-NR^9R^{10}$ together represents a saturated 5 or 6 membered azacyclic ring;

R^{11} represents H or C1 to 4 alkyl;

n represents an integer 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

Particular compounds according to the present invention include:

5-bromo-3-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-(3-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile;

5-bromo-2-(2-furyl)-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

3-{4-[5-bromo-2-(2-furyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]phenoxy}-*N*,*N*-dimethylpropan-1-amine;

5-bromo-3-(4-morpholin-4-ylphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-2,3-diphenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-2-(4-bromophenyl)-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-2,3-bis(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine;

N-(3-{4-[5-bromo-2-(2-furyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]phenoxy}propyl)-*N*,*N*-dimethylamine;

5-bromo-3-phenyl-2-(1,3-thiazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-furan-2-yl-1-*H*-pyrrolo[2,3-*b*]pyridine;

N-[5-(5-bromo-2-phenyl-1-*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-fuan-2-ylmethyl]-acetamide;

5-bromo-3-(5-aminomethylfuran-2-yl)-2-phenyl-1H-pyrrolo[2,3-*b*]pyridine;

5-bromo-2,3-difuran-2-yl-1*H*-pyrrolo[2,3-*b*]pyridine;

methyl 5-(5-bromo-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-pyrrole-2-carboxylate;

5-bromo-3-phenyl-2-(1H-pyrrol-3-yl)-1H-pyrrolo[2,3-b]pyridine;

5-bromo-3-phenyl-2-(1,3-oxazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine;

3-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol;

1-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-3-[(2-pyrrolidin-1-ylethyl)amino]propan-2-ol;

1-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-3-pyrrolidin-1-ylpropan-2-ol;

5-bromo-3-{4-[2-(1-methylpyrrolidin-2-yl)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-2-phenyl-3-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-[4-(2-morpholin-4-ylethoxy)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-[3-(2-morpholin-4-ylethoxy)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

3-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-*N*,*N*-dimethylpropan-1-amine;

5-bromo-3-{4-[2-(2-methoxyethoxy)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-{3-[2-(1-methylpyrrolidin-2-yl)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

3-{4-[3-(dimethylamino)propoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

5-{[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]methyl}-1,3-oxazolidin-2-one;

3-{4-[3-(dimethylamino)propoxy]phenyl}-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

(3-{4-[5-bromo-2-(4-methoxy-phenyl)-1*H*-pyrrolo[1,3-*b*]pyridin-3-yl]-phenoxy}-propyl)-dimethylamine;

3-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]propan-1-amine;

5-bromo-3-(4-aminomethylphenyl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine;

5-bromo-3-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine;

5-bromo-3-[4-(4,4-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

N-(2-aminoethyl)-4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide;

3-[[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzyl](1,2-dihydroxypropyl)amino]propane-1,2-diol;

4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid;

N^5-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzyl]glutamine;

3-(4-hydroxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

3-[4-(aminomethyl)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

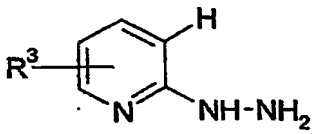
3-(4-morpholin-4-ylphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

3-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

5-bromo-2-(4-methoxy-phenyl)-3-piperazin-1-yl-1H-pyrrolo[2,3-b]pyridine;
5-bromo-2-(4-methoxyphenyl)-3-(4-methylpiperazin-1-yl)-1H-pyrrolo[2,3-b]pyridine;
4-[5-bromo-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester;
5-bromo-2-(4-methoxyphenyl)-3-morpholin-4-yl-1H-pyrrolo[2,3-*b*]pyridine;
5-bromo-3-(4-methanesulfonylpiperazin-1-yl)-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine;
4-[5-bromo-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-piperazine-1-carbaldehyde;
5-bromo-2-phenyl-3-pyrrol-1-yl-1H-pyrrolo[2,3-b]pyridine;
5-cyano-2-(4-methoxy-phenyl)-3-pyrrol-1-yl-1H-pyrrolo[2,3-b]pyridine;
5-bromo-3-(2,5-dimethyl-pyrrol-1-yl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine;
3-(4-methoxyphenyl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile;
and pharmaceutically acceptable salts thereof.

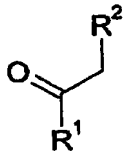
The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

In a further aspect the invention provides a process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

in which R^3 is as defined in formula (I), with a compound of formula (III):



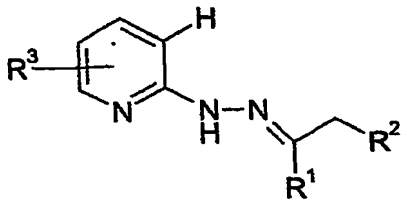
(III)

in which R^1 and R^2 are as defined in formula (I);

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

The process may be carried out by heating together at a suitable temperature and preferably in an inert atmosphere the compounds of formulae (II) and (III), optionally in the presence of an inert solvent. Preferably the reaction is carried out at a temperature between 100 °C and 250 °C, preferably in the absence of a solvent. Suitable reaction times are generally from 5 minutes to 3 hours.

Alternatively the process may be carried out in two steps. In the first step, the compounds of formulae (II) and (III) are condensed together to give an intermediate hydrazone of formula (IV)



(IV)

wherein R^1, R^2 and R^3 are as defined in formula (I).

And in a second step the hydrazone (IV) is cyclised by heating under similar conditions to those used for the single step process above. The condensation of compounds of formulae (II) and (III) to give the hydrazone (IV) is generally carried out in an inert solvent such as benzene or toluene in the presence of an acid catalyst such as acetic acid or p-toluenesulphonic acid with removal of water by azeotropic distillation.

Compounds of formula (I) in which R^2 represents an aromatic ring substituted by a group –W-X-Y may, when W represents O, be prepared by alkylation of the corresponding compound wherein the aromatic ring is substituted by OH, using reactions that will be readily apparent to the man skilled in the art. Some typical such reactions are illustrated within the Examples disclosed herein.

Salts of compounds of formula (I) may be formed by reacting the free base or a salt, enantiomer, tautomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble, or in a solvent in which the salt is soluble followed by subsequent removal of the solvent *in vacuo* or by freeze drying. Suitable solvents include, for example, water, dioxan, ethanol, 2-propanol, tetrahydrofuran or diethyl ether, or mixtures thereof. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

Compounds of formula (I) and intermediate compounds thereto may be prepared as such or in protected form. The protection and deprotection of functional groups is, for example,

described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1999).

The compounds of the invention and intermediates may be isolated from their reaction mixtures, and if necessary further purified, by using standard techniques.

The compounds of formula (I) may exist in enantiomeric or diastereoisomeric forms or mixtures thereof, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation or HPLC. Alternatively, the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions that will not cause racemisation.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures thereof.

According to a further aspect of the invention we provide a compound of formula (I) or a pharmaceutically acceptable salts thereof, for use as a medicament.

The compounds of formula (I), and their pharmaceutically acceptable salts are useful because they possess pharmacological activity in animals. The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of kinase activity, especially Itk kinase activity, and as such are predicted to be useful in therapy. They may be used in the treatment or prophylaxis of allergic, autoimmune, inflammatory, proliferative and hyperproliferative diseases and immune-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

Thus, another aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or conditions in which inhibition of Itk activity is

beneficial; and a method of treating, or reducing the risk of, diseases or conditions in which inhibition of Itk activity is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Examples of these conditions are:

(1) **(the respiratory tract)** airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (for example, late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia; sinusitis, chronic rhinosinusitis, nasosinusal polyposis; pulmonary fibrosis;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, for example, migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; tuberculosis;

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

We are particularly interested in Th2-driven and/or mast cell-driven and/or basophil-driven conditions or diseases.

Thus, a more particular aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of Th2-driven and/or mast cell-driven and/or basophil driven diseases or conditions; and a method of treating, or reducing the risk of, Th2-driven and/or mast cell-driven and/or basophil driven diseases or conditions which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a preferred aspect of the invention, we provide a method for the treatment or prevention of a reversible obstructive airway disease, especially asthma, which comprises administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a human that is suffering from or susceptible to the disease. We also provide the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of a reversible obstructive airway disease, especially asthma.

In another preferred aspect of the invention, we provide a method for the treatment or prevention of rhinitis which comprises administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a human that is suffering from or susceptible to rhinitis, especially allergic rhinitis. We also provide the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of rhinitis, especially allergic rhinitis.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

For the above mentioned therapeutic indications, the dose of the compound to be administered will depend on the compound employed, the disease being treated, the mode of administration, the age, weight and sex of the patient. Such factors may be determined by the attending physician. However, in general, satisfactory results are obtained when the compounds are administered to a human at a daily dosage of between 0.1 mg/kg to 100 mg/kg (measured as the active ingredient).

The compounds of formula (I) may be used on their own, or in the form of appropriate pharmaceutical formulations comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse reaction, for example, an allergic reaction. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

According to the invention, there is provided a pharmaceutical formulation comprising preferably less than 95% by weight and more preferably less than 50% by weight of a compound of formula (I) in admixture with a pharmaceutically acceptable diluent or carrier.

We also provide a method of preparation of such pharmaceutical formulations that comprises mixing the ingredients.

The compounds may be administered topically, for example, to the lungs and/or the airways, in the form of solutions, suspensions, HFA aerosols or dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, for example, by oral administration in the form of tablets, pills, capsules, syrups, powders or granules; or by parenteral administration, for example, in the form of sterile parenteral solutions or suspensions; or by rectal administration, for example, in the form of suppositories.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 μm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_8-C_{20} fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable

carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound, with or without a carrier substance, is delivered to the patient.

For oral administration the active compound may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may

contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The following Examples are intended to illustrate, but in no way limit the scope of the invention.

General methods All reactions were performed in dried glassware in an argon atmosphere at room temperature, unless otherwise noted. All reagents and solvents were used as received. Merck Silica gel 60 (0.040-0.063 mm) was used for preparative silica gel chromatography. A Kromasil KR-100-5-C18 column (250 x 20 mm, Akzo Nobel) and mixtures of acetonitrile/water at a flow rate of 10 ml/min was used for preparative HPLC. Reactions were monitored at 254 nm by analytical HPLC, using a Kromasil C-18 column (150 x 4.6 mm) and a gradient (containing 0.1% trifluoroacetic acid) of 5 to 100% of acetonitrile in water at a flow rate of 1 ml/min. Evaporations of solvents were performed under reduced pressure using a rotary evaporator at a maximum temperature of 60°C. Products were dried under reduced pressure at about 40 °C.

^{1}H-NMR spectra were recorded on a Varian Inova 400 MHz or Varian Mercury 300 MHz instrument. The central solvent peak of chloroform-*d* (δ_H 7.27 ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or methanol-d_4 (δ_H 3.35 ppm) were used as internal references. Low resolution mass spectra were obtained on a Hewlett Packard 1100 LC-MS system equipped with a APCI ionisation chamber.

Preparation 1

N-(5-Cyano-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetamide

The title compound (430 mg, 26%) was synthesized from N-(2-oxo-2-phenyl-ethyl)-acetamide (900 mg, 5 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (900 mg, 5 mmol) essentially as described in Example 1.

^{1}H-NMR (DMSO-d_6): δ 12.20 (1H, s); 9.56 (1H, s), 8.29 (1H, s); 7.93 (1H, s); 7.82 (2H, d); 7.50 (2H, t); 7.39 (1H, t); 2.09 (3H, s).

APCI-MS m/z: 330 [MH+].

Preparation 2

N-(5-Cyano-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetamide

6-Chloro-nicotinonitrile (1.38 g, 10 mmol) was dissolved in 1,4-dioxane (50 ml). Hydrazine hydrate (0.525 ml, 10.4 mmol) was added and the resulting solution stirred for 1.5h, whereupon it was concentrated *in vacuo*. The residue was chromatographed (silica gel, gradient ethyl acetate/heptane from 1:1 to 1:0). The slower running component was concentrated *in vacuo* to afford the 6-hydrazino-nicotinonitrile monohydrate [0.80 g, 53%, APCI-MS m/z: 135.2 [MH+]]. Part of this hydrazine (67 mg, 0.5 mmol) and N-(2-oxo-2-phenyl-ethyl)-acetamide (85 mg, 0.5 mmol) were fused together for 1h at 230 °C. The reaction mixture was allowed to cool and the glassy solid suspended in warm dichloromethane/methanol (7:3 mixture) and then filtered. The solid was further washed with hot acetonitrile/N,N-dimethylformamide (9:1 mixture) and finally acetonitrile. This afforded the title compound as a grey powder (25 mg, 18%).

^{1}H-NMR (DMSO-d_6): δ 12.64 (1H, s); 9.66 (1H, s); 8.62 (1H, s); 8.27 (1H, s); 7.84 (2H, d); 7.52 (2H, t); 7.42 (1H, t); 2.10 (3H, s).

^{13}C-NMR (DMSO-d_6): δ 147.3; 145.8; 134.0; 131.5; 129.9; 128.8; 128.7; 127.5; 118.8; 117.6; 110.1; 99.9; 22.7.

APCI-MS m/z: 277.1 [MH+].

Preparation 3

5-Bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-ylamine

N-(5-Bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-acetamide (200 mg, 0.6 mmol) was suspended in concentrated hydrochloric acid (20 ml) and heated to reflux overnight. The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by filtration. This solid was again suspended in water (20 ml) and treated with saturated aqueous sodium hydrogen carbonate until the suspension was neutral. The precipitate was isolated by filtration and thoroughly washed with water to yield the title compound as a yellow powder (170 mg, 97%).

^{1}H-NMR (DMSO-d_6): δ 12.36 (1H, s); 9.60 (2H, bs); 8.59 (1H, s); 8.34 (1H, s); 7.85 (2H, d); 7.54 (2H, t); 7.45 (1H, t).

APCI-MS m/z: 288.2/292.2 [M+].

Example 1

5-Bromo-3-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine

Under an inert atmosphere 2-(4-methoxyphenyl)-1-phenylethanone (3.16 g, 13.9 mmol) and 5-bromo-2-hydrazinopyridine (2.62 g, 13.9 mmol) were fused together at 230 °C for 70 minutes. After cooling the crude product was crystallized from acetonitrile to give the title compound (3.05 g, 58%).

^{1}H-NMR (DMSO-d_6): δ 11.60-12.80 (1H, bs); 8.29 (1H, d); 7.89 (1H, d); 7.44-7.48 (2H, m); 7.28-7.37 (3H, m); 7.21 (2H, d); 6.94 (2H, d); 3.87 (3H, s).

APCI-MS m/z: [MH+].

Following the general method of Example 1, the compounds of Examples 2 to 11 were prepared:

Example 2

5-Bromo-3-(3-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine

The title compound (1.62 g, 36 %) was synthesized from 2-(3-methoxyphenyl)-1-phenylethanone (2.72 g, 12.0 mmol) and 5-bromo-2-hydrazinopyridine (2.26 g, 12.0 mmol).

^{1}H-NMR (DMSO-d_6): δ 11.00-13.00 (2H, bs); 8.32 (1H, d); 7.98 (1H, d); 7.42-7.51 (2H, m); 7.23-7.41 (5H, m); 6.81-6.92 (3H, m); 3.65 (3H, s).

Example 3

4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile

The title compound (1.98 g, 35 %) was synthesized from 4-(2-oxo-2-phenylethyl)benzonitrile (3.46 g, 15.6 mmol) and 5-bromo-2-hydrazinopyridine (2.86 g, 15.2 mmol).

^{1}H-NMR (DMSO-d_6): δ 12.60 (1H, s); 8.36 (1H, d); 8.11 (1H, d); 7.82 (2H, d); 7.51 (2H, d); 7.38-7.48 (5H, m).

APCI-MS m/z: 374.1/376.0 [MH+].

Example 4

5-Bromo-2-(2-furyl)-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine

The title compound (416 mg, 25 %) was synthesized from 1-(2-furyl)-2-phenylethanone (884 mg, 5.0 mmol) and 5-bromo-2-hydrazinopyridine (942 mg, 5.0 mmol).

^{1}H-NMR (DMSO-d_6): δ 12.50 (1H, d); 8.32 (1H, d); 7.89 (1H, d); 7.63 (1H, d); 7.44-7.48 (5H, m); 6.78 (1H, d); 6.59 (1H, dd).

APCI-MS m/z: 339.0 /341.0 [MH+].

Example 5

3-{4-[5-Bromo-2-(2-furyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]phenoxy}-*N*,*N*-dimethylpropan-1-amine trifluoroacetate

The title compound (2.9 mg, 0.6 %) was synthesized from N-(2-oxo-2-phenyl-ethyl)-acetamide (253 mg, 0.89 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (165 mg, 0.88 mmol) and purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1).

APCI-MS m/z: 440.1/442.1 [MH+].

Example 6

5-Bromo-3-(4-morpholin-4-ylphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine

The title compound (67 mg, 29 %) was synthesized from 2-(4-morpholin-4-ylphenyl)-1-phenylethanone (150 mg, 0.53 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (100 mg, 0.53 mmol).

^{1}H-NMR (DMSO-d_6): δ 12.21 (1H, s); 8.24 (1H, d); 7.88 (1H, d); 7.27-7.44 (7H, m); 6.90 (2H, d); 3.70 (4H, dd); 3.14 (4H, dd).

APCI-MS m/z: 434.1/436.1 [MH+].

Example 7

5-Bromo-2,3-diphenyl-1*H*-pyrrolo[2,3-*b*]pyridine

The title compound (68 mg, 37 %) was synthesized from 1,2-diphenylethanone (104 mg, 0.53 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (100 mg, 0.53 mmol).

^{1}H-NMR (DMSO-d_6): δ 12.38 (1H, bs); 8.34 (1H, d); 7.98 (1H, d); 7.48 (2H, dd); 7.29-7.43 (8H, m).

APCI-MS m/z: 349.0/351.0 [MH+].

Example 8

5-Bromo-2-(4-bromophenyl)-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine

The title compound (89 mg, 39 %) was synthesized from 1-(4-bromophenyl)-2-phenylethanone (146 mg, 0.53 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (100 mg, 0.53 mmol).

^{1}H-NMR (DMSO-d_6): δ 12.36 (1H, bs); 8.36 (1H, d); 7.99 (1H, d); 7.60 (2H, d); 7.31-7.45 (7H, m).

APCI-MS m/z: 426.1/427.1/428.1/429.1 [MH+].

Example 9

5-Bromo-2,3-bis(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine

The title compound (66 mg, 30 %) was synthesized from 1,2-bis(4-methoxyphenyl)ethanone (136 mg, 0.53 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (100 mg, 0.53 mmol).

^{1}H-NMR (DMSO-d_6): δ 12.22 (1H, bs); 8.28 (1H, d); 7.88 (1H, d); 7.42 (2H, d); 7.25 (2H, d); 6.92-7.01 (4H, m); 3.28-3.36 (6H, m).

APCI-MS m/z: 349.0/351.0 [MH+].

Example 10

N-(3-{4-[5-Bromo-2-(2-furyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]phenoxy}propyl)-*N*,*N*-dimethylamine trifluoroacetate

The title compound (4.0 mg, 1.0 %) was synthesized from 2-{4-[3-(dimethylamino)propoxy]phenyl}-1-(2-furyl)ethanone (239 mg, 0.83 mmol) and 6-hydrazinonicotinonitrile (111 mg, 0.83 mmol) and purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1).

APCI-MS m/z: 387.2 [MH+].

Example 11

5-Bromo-3-phenyl-2-(1,3-thiazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

The title compound (51 mg, 6 %) was synthesized from 1-(1,3-thiazol-2-yl)-2-phenylethanone (470 mg, 2.3 mmol) and 5-bromo-2-hydrazinopyridine (439 mg, 2.3 mmol).

^{1}H-NMR (DMSO-d_6): δ 8.41 (1H, d); 7.96 (1H, d); 7.88 (1H, d); 7.73 (1H, d); 7.56-7.46 (5H, m); 7.1 (1H, br s).

APCI-MS m/z: 355.9 /357.9 [MH+].

Example 12

5-Bromo-3-furan-2-yl-1-*H*-pyrrolo[2,3-*b*]pyridine

(5-Bromo-pyridin-2-yl)-hydrazine (1.96 g, 10 mmol) and 2-furan-2-yl-1-phenylethanone (2.05 g, purity 86%, 9.5 mmol) in benzene (40 mL) containing p-toluenesulfonic acid (50 mg) was heated at reflux temperature. Water was continuously distilled off using a Dean-Stark trap. After 16h, the reaction mixture was cooled, dichloromethane was added and the mixture was washed with saturated aqueous sodium hydrogen carbonate, brine and evaporated. Crystallization from diethyl ether-heptane gave *N*-(5-bromopyridin-2-yl)-*N'*-(2-furan-2-yl-1-phenylethylidene)-hydrazine (1.86 g, 55%). M.p. 105-107 °C.

^{1}H-NMR (DMSO-d_6): δ 10.32 (1H, s); 8.24 (1H, dd); 7.87-7-82 (3H, m); 7.51 (1H, dd); 7.41-7.36 (2H, m); 7.35-7.29 (2H, m); 6.33 (1H, dd); 6.18 (1H, dd); and 4.35 (2H, s) ppm.

APCI-MS m/z: 356.1/358.1 [MH+].

N-(5-Bromopyridin-2-yl)-*N'*-(2-furan-2-yl-1-phenylethylidene)-hydrazine (440 mg, 1.14 mmol) was stirred in an inert atmosphere at 225 °C for 10 minutes. The crude product was purified with column chromatography (silica gel, ethyl acetate/heptane 1:3) to give the title compound (27 mg, 6.4 %) and a second fraction containing additional, slightly impure material (42 mg).

^{1}H-NMR (DMSO-d_6): δ 12.52 (1H, s); 8.37 (1H, d); 8.28 (1H, d); 7.68 (1H, dd); 7.63-7.58 (2H, m); 7.53-7.44 (3H, m); 6.55 (1H, dd); 6.45 (1H, dd).

APCI-MS m/z: 339.1/341.1 [MH+].

Example 13

N-[5-(5-Bromo-2-phenyl-1-*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-fuan-2-ylmethyl]-acetamide

C-(2,5-Dimethoxy-2,5-dihydrofuran-2-yl)-methylamine (5 g, 31.6 mmol) was acetylated by stirring in a mixture of acetic anhydride (15 mL) and pyridine (25 mL) at ambient temperature for 18h. Repeated co-evaporation with toluene and triturating the residue with diethyl ether gave *N*-(2,5-dimethoxy-2,3-dihydrofuran-2-ylmethyl)-acetamide (2.0 g, 31 %).

^{1}H-NMR ($CDCl_3$): δ 7.28 (1H, s); 6.09 (1H, dd); 5.92 (1H, dd); 5.80-5.70 (1H, b); 5.50 (1H, t); 3.64 (1H, dd); 3.53 (3H, s); 3.44 (1H, dd); 3.23 (3H, s); 1.99 (3H, s).

A mixture of ethyl 3-oxo-3-phenylpropionate (1.88 g, 9.8 mmol) and zinc chloride (0.94 g, 6.9 mmol) in acetic acid (0.41 mL) and water (1.88 mL) was heated at 110 °C. Then *N*-(2,5-dimethoxy-2,5-dihydrofuran-2-ylmethyl)-acetamide (1.91 g, 9.5 mmol) was added in portions during 5 minutes. The reaction mixture was stirred for an additional 5 minutes at 110 °C and was then cooled and partitioned between toluene (20 mL) and water (20 mL). The organic phase was washed with water and brine and then evaporated. Chromatography (silica gel, ethyl acetate-heptane 3:1) gave a mixture (2.42 g) of 2-[5-(acetylaminomethyl)-furan-2-yl]-3-oxo-3-phenylpropionic acid ethyl ester and the corresponding carboxylic acid as an oil. A mixture of this material (2.3 g), lithium chloride (8.85 g), acetic acid (0.7 mL) in *N*-methylpyrrolidinone (2.1 mL) was stirred at reflux temperature for 22h. The reaction mixture was then diluted with ethyl acetate, washed twice with water and evaporated. Triturating the residue with diethyl ether gave *N*-[5-(2-oxo-2-phenylethyl)-furan-2-ylmethyl]-acetamide (0.98 g, 42 %).

^{1}H-NMR (DMSO-d_6): δ 8.26 (1H, bt); 8.02 (2H, d); 7.66 (1H, tt); 7.54 (2H, t); 6.21 (1H, d); 6.16 (1H, d); 4.43 (2H, s); 4.18 (2H, d); 1.82 (3H, s).

APCI-MS m/z: 258.2 [MH+].

(5-Bromo-pyridin-2-yl)-hydrazine (0.75 g, 4 mmol) and *N*-[5-(2-oxo-2-phenylethyl)-furan-2-ylmethyl]-acetamide (0.98 g, 3.8 mmol) in benzene (40 mL) containing p-toluenesulfonic acid (50 mg) was heated at reflux temperature. Water was continuously distilled off using a Dean-Stark trap. After 2h, the reaction mixture was cooled, toluene was added and the mixture was washed with saturated aqueous sodium hydrogen carbonate solution, water and brine. Evaporation and crystallisation of the residue from ethyl acetate gave the *N*-(5-{2-[(5-bromopyridin-2-yl)-hydrazono]-2-phenylethyl}-furan-2-ylmethyl)-acetamide (0.77 g, 47 %). M.p. 176-176.5 °C.

^{1}H-NMR (DMSO-d_6 + D_2O): δ 8.28 (1H, bt); 8.20 (1H, d); 7.85-7.78 (3H, m); 7.41-7.27.(4H, m); 6.08 (1H, d); 5.99 (1H, d); 4.25 (2H, s); 4.12 (2H, s) and 1.78 (3H, s).
APCI-MS m/z: 427.2/429.2 [MH+].

N-(5-{2-[(5-Bromopyridin-2-yl)-hydrazono]-2-phenylethyl}-furan-2-ylmethyl)-acetamide (522 mg, 1.22 mmol) was stirred in an inert atmosphere at 225 °C for 16 minutes, cooled and then triturated with ethyl acetate to give the title compound (151 mg, 30 %).

^{1}H-NMR (DMSO-d_6): δ 12.49 (1H, s); 8.37-8.29 (2H, m); 7.70-7.00 (1H, b); 7.68-7.62 (2H, m); 7.53-7.43 (3H, m); 6.29 (1H, d); 6.26 (1H, d); 4.27 (2H, d); 1.86 (3H, s).
APCI-MS m/z: 410.1/412.1 [MH+].

Example 14

5-Bromo-3-(5-aminomethylfuran-2-yl)-2-phenyl-1H-pyrrolo[2,3-*b*]pyridine

A mixture of *N*-[5-(5-bromo-2-phenyl-1-*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-furan-2-ylmethyl]-acetamide (75 mg, 0.18 mmol), methanol (10 mL) and aqueous potassium hydroxide (10 mL, 3M) was refluxed overnight. The methanol was evaporated off and the precipitate was washed with water by repeated centrifugations and dried to give crude title compound (purity 91 %) which was further purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1). Acetonitrile was evaporated and the resulting aqueous emulsion was made alkaline with saturated aqueous sodium hydrogen carbonate and extracted three times with dichloromethane.

Evaporation of the dichloromethane at reduced pressure gave the title compound as a yellow solid (16 mg, 23 %).

^{1}H-NMR (DMSO-d_6): δ 8.35 (1H, d); 8.30 (1H, d); 7.66-7.62 (2H, m); 7.51-7.42 (3H, m); 6.31 (1H, d); 6.25 (1H, bd); 3.67 (2H, s).

^{13}C-NMR (DMSO-d_6): δ 156.2; 146.5; 146.2; 143.4; 136.7; 131.1; 129.5; 128.70; 128.65 (2C); 128.3 (2C); 120.4; 111.5; 106.9; 106.3; 102.1; 38.8.

APCI-MS m/z: 369.1/371.1 [MH+]; 351.1/353.1 [MH+ -NH_2].

Example 15

5-Bromo-2,3-difuran-2-yl-1*H*-pyrrolo[2,3-*b*]pyridine

1,2-Di-furan-2-yl-ethanone (1.02 g, 5.8 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (1.09 g, 5.8 mmol) in benzene (40 mL) containing acetic acid (0.4 mL) was heated at reflux temperature for 20h. Water was continuously distilled off using a Dean-Stark trap. Crude, impure title compound was crystallized from the reaction mixture at 8 °C. This material (505 mg) was heated in an inert atmosphere at 230 °C for 7 minutes and then partitioned between toluene and water. The toluene phase was washed with water and brine and then evaporated. The residue was chromatographed (silica gel; ethyl acetate-heptane 1:3) to give the title compound (47 mg, 2.5 %).

^{1}H-NMR (DMSO-d_6): δ 12.59 (1H, s); 8.36 (1H, d); 8.30 (1H, d); 7.91 (1H, dd); 7.80 (1H, dd); 7.10 (1H, dd); 6.84 (1H, dd); 6.71 (1H, dd); 6.64 (1H, dd).

APCI-MS m/z: 321.1/331.1 [MH+].

Example 16

Methyl 5-(5-bromo-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-pyrrole-2-carboxylate

(5-Bromo-pyridin-2-yl)-hydrazine (378 mg, 2 mmol) and 4-phenylacetyl-1H-pyrrole-2-carboxylic acid methyl ester (488 mg, 2 mmol) were fused together at 220 °C for 1h. After cooling the crude product was crystallized from acetonitrile and further purified by

preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the title compound (5 mg, 0.6%).

^{1}H-NMR (DMSO-d_6): δ 12.17 (1H, bs); 12.13 (1H, bs); 8.22 (1H, s); 7.74 (1H, s); 7.50-7.36 (5H, m); 7.22 (1H, s); 6.94 (1H, s); 3.73 (3H, s).

APCI-MS m/z: 396.3 [MH+].

Example 17

5-Bromo-3-phenyl-2-(1H-pyrrol-3-yl)-1H-pyrrolo[2,3-b]pyridine

(5-Bromo-pyridin-2-yl)-hydrazine (378 mg, 2 mmol) and 4-phenylacetyl-1H-pyrrole-2-carboxylic acid methyl ester (488 mg, 2 mmol) were fused together at 220 °C for 1h. After cooling the crude product was crystallized from acetonitrile, purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) and further chromatographed (silica gel, ethyl acetate/heptane 1:1) to give the title compound (3 mg, 0.4%).

^{1}H-NMR (DMSO-d_6): δ 11.95 (1H, s); 11.02 (1H, bs); 8.16 (1H, s); 7.69 (1H, s); 7.50-7.40 (4H, m); 7.35 (1H, m); 7.08 (1H, d); 6.73 (1H, m); 6.19 (1H, t).

APCI-MS m/z: 338.1 [MH+].

Example 18

5-Bromo-3-phenyl-2-(1,3-oxazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine

Oxazole (1.6 ml, 24.3 mmol) was dissolved in dry tetrahydrofuran (60 ml). Butyl lithium (1.6M in hexane, 14.5 ml) was slowly added at –25 °C, after which the temperature was allowed to rise to 0 °C. TMSOTf (4.19 ml, 23.2 mmol) was slowly added and the mixture stirred at room temperature for 20 minutes. Phenylacetylchloride (3.06 ml, 23.1 mmol) was slowly added and the mixture stirred for 3.5 h. Water (20 ml) was added, and the mixture was extracted with dichloromethane. Drying (Na_2SO_4) and evaporation delivered crude

material which was purified by column chromatography (silica gel, dichloromethane), affording the 1-(1,3-oxazol-2-yl)-2-phenylethanone as a yellow oil (0.631 g, 14 %).
1H-NMR ($CDCl_3$): δ 7.83 (1H, d); 7.40-7.25 (6H, m); 4.38 (2H, s).
APCI-MS m/z: 188 [MH+].

1-(1,3-Oxazol-2-yl)-2-phenylethanone (631 mg, 3.4 mmol) and 5-bromo-2-hydrazinopyridine (634 mg, 3.4 mmol) were fused together at 220 °C for 1h to give the title compound (332 mg, 29 %).
^{1}H-NMR (DMSO-d_6): δ 12.93 (1H, s); 8.46 (1H, d); 8.21 (1H, s); 8.04 (1H, d); 7.57-7.37 (6H, m).
APCI-MS m/z: 339.9 /341.9 [MH+].

Example 19

3-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol

5-Bromo-3-(3-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.41 g, 3.72 mmol) and concentrated aqueous HBr (30 ml) were heated at 120 °C for 64h under an inert atmosphere. After cooling and basification with aqueous ammonia the product was filtered off, washed with water and dried *in vacuo* to give the title compound (1.34 g, 99%).
^{1}H-NMR (DMSO-d_6): δ 12.37 (1H, s); 9.38 (1H, bs); 8.31 (1H, d); 7.93 (1H, d); 7.46-7.52 (2H, m); 7.22-7.41 (3H, m); 7.18 (1H, dd); 6.63-6.76 (3H, m).

Example 20

3-(4-Methoxyphenyl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile

The title compound (25 mg, 11%) was synthesized from 6-hydrazino-nicotinonitrile (90 mg, 0.67 mmol), and 1-(4-methoxyphenyl)-2-phenylethanone (152 mg, 0.67 mmol) essentially as described in Example 1 and purified by column chromatography (silica gel; dichloromethane/methanol gradient from 1:0 to 7:3) and crystallized from acetonitrile.

^{1}H-NMR (DMSO-d_6): δ 12.74 (1H, bs); 8.64 (1H, s); 8.28 (1H, s); 7.50 (2H, d); 7.41-7.34 (3H, m); 7.27 (2H, d); 6.97 (2H, d); 3.78 (3H, s).

^{13}C-NMR (DMSO-d_6): δ 158.1; 148.9; 145.7; 136.5; 131.1; 130.7; 130.6; 128.5; 128.4; 124.8; 119.7; 118.7; 114.3; 112.2; 100.3; 55.0.

APCI-MS m/z: 326.4 [MH+].

Example 21

1-[4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-3-[(2-pyrrolidin-1-ylethyl)amino]propan-2-ol dihydrochloride

a) 4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol

The title compound (1.05 g, 93 %) was synthesized from 5-bromo-3-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.17 g, 2.9 mmol) essentially as described in Example 19.

^{1}H-NMR (DMSO-d_6): δ 12.25 (1H, bs); 9.43 (1H, b); 8.29 (1H, d); 7.89 (1H, d); 7.46-7.51 (2H, m); 7.28-7.39 (3H, m); 7.11 (2H, d); 6.78 (2H, d).

APCI-MS m/z: 365.0/367.0 [MH+].

b) 1-[4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-3-[(2-pyrrolidin-1-ylethyl)amino]propan-2-ol dihydrochloride

A mixture of 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (174 mg, 0.48 mmol), sodium hydride (60% suspension in mineral oil, 86 mg, 2.14 mmol) and N,N-dimethylformamide (2 ml) was heated at 60 °C for 30 minutes. Epibromohydrin (66 mg, 0.48 mmol) was added and the reaction mixture was further stirred at 60 °C for 1h. 2-Pyrrolidin-1-ylethanamine (76 mg, 0.68 mmol) was added and reaction was heated at 60 °C for 14h. Water (1 ml) was added and mixture was eluted through silica gel with dichloromethane /methanol/aqueous ammonia (79.5/20/0.5) and the product was further purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the title compound (3 mg, 1 %).

APCI-MS m/z: 535.0/537.0 [MH+].

Example 22

1-[4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-3-pyrrolidin-1-ylpropan-2-ol trifluoroacetate.

The title compound (6 mg, 4 %) was synthesized from 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (82 mg, 0.22 mmol), epibromohydrin and pyrrolidin-3-ol (99 mg, 1.13 mmol) essentially as described in Example 21.
APCI-MS m/z: 508.0/510.1 [MH+].

Example 23

5-Bromo-3-{4-[2-(1-methylpyrrolidin-2-yl)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine trifluoroacetate

A mixture of 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (100 mg, 0.27 mmol), sodium hydride (60% suspension in mineral oil, 45 mg, 1.25 mmol) and N,N-dimethylformamide (2 ml) was heated at 60 °C for 30 minutes. A mixture of 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (51 mg, 0.28 mmol), sodium hydride (60% suspension in mineral oil, 15 mg, 0.42 mmol) and N,N-dimethylformamide (500 µl) was added and the reaction mixture was further stirred at 60 °C for 75 minutes. Water (1 ml) and acetic acid (200 µl, 3.5 mmol) were added and the product was purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the title compound (73 mg, 45 %).
^{1}H-NMR (CD_3CN): δ 10.37 (sH, s); 8.33 (1H, d); 8.03 (1H, d); 7.46-7.53 (2H, m); 7.37-7.43 (3H, m); 7.23-7.33 (2H, m); 6.94-7.10 (2H, m); 4.68-4.80 (1H, m); 4.10-4.36 (2H, m); 3.32-3.75 (3H, m); 2.85-3.22 (2H, m); 1.80-2.44 (6H, m).
APCI-MS m/z: 476.0/478.0 [MH+].

Following the general method of Example 23, the compounds of Examples 24 to 33 were prepared:

Example 24

5-Bromo-2-phenyl-3-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine trifluoroacetate

The title compound (21 mg, 18%) was synthesized from 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (75 mg, 0.21 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride
(35 mg, 0.21 mmol).
^{1}H-NMR (CD_3CN): δ 11.12 (1H, s); 8.42 (1H, d); 8.18 (1H, d); 7.41-7.53 (5H, m); 7.10 (2H, d); 6.75 (2H, d); 4.50 (2H, dd); 3.66-3.78 (2H, m); 3.34-3.51 (2H, m); 2.82-2.95 (2H, m); 2.30-2.60 (4H, m).
APCI-MS m/z: 462.1/464.1 [MH+].

Example 25

5-Bromo-3-[4-(2-morpholin-4-ylethoxy)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine trifluoroacetate

The title compound (59 mg, 36%) was synthesized from 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (100 mg, 0.27 mmol) and 4-(2-chloroethyl)morpholine hydrochloride
(53 mg, 0.28 mmol).
^{1}H-NMR (CD_3CN): δ 8.31 (1H, d); 8.00 (1H, d); 7.28-7.54 (7H, m); 7.01-7.12 (2H, m); 4.36-4.50 (2H, m); 3.84-4.26 (2H, m); 3.52-3.68 (4H, m); 3.20-3.45 (4H, m).
APCI-MS m/z: 478.0/480.0 [MH+].

Example 26

5-Bromo-3-[3-(2-morpholin-4-ylethoxy)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine trifluoroacetate

The title compound (13.5 mg, 8%) was synthesized from 3-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (101 mg, 0.27 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (51 mg, 0.27 mmol).

APCI-MS m/z: 478.0/480.0 [MH+].

Example 27

3-[4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxyl-*N*,*N*-dimethylpropan-1-amine trifluoroacetate

The title compound (37 mg, 34%) was synthesized from 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (100 mg, 0.27 mmol) and *N*-(3-chloropropyl)-*N*,*N*-dimethylamine hydrochloride (44 mg, 0.28 mmol).

^{1}H-NMR (CD_3CN): δ 8.34 (1H, d); 8.03 (1H, d); 7.38-7.44 (5H, m); 7.31 (2H, d); 6.98 (2H, d); 4.17-4.30 (2H, m); 3.43-3.64 (2H, m); 2.64-2.88 (6H, m); 2.34-2.58 (2H, m).

APCI-MS m/z: 450.0/452.0 [MH+].

Example 28

5-Bromo-3-{4-[2-(2-methoxyethoxy)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine

The title compound (68 mg, 53%) was synthesized from 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (100 mg, 0.27 mmol) and 1-bromo-2-(2-methoxyethoxy)ethane (51 mg, 28 mmol).

^{1}H-NMR (CD_3Cl: δ 12.08 (1H, s); 8.24 (1H, m); 8.08 (1H, d); 7.56-7.61 (2H, m); 7.38-7.47 (3H, m); 7.32 (2H, d); 6.98 (2H, d); 4.22 (2H, dd); 3.93 (2H, dd); 3.78 (2H, dd); 3.63 (2H, dd); 3.44 (3H, s).

APCI-MS m/z: 466.9/469.0 [MH+].

Example 29

5-Bromo-3-{3-[2-(1-methylpyrrolidin-2-yl)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine trifluoroacetate

The title compound (65 mg, 40%) was synthesized from 3-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (101 mg, 0.27 mmol) and 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (51 mg, 0.28 mmol).
APCI-MS m/z: 476.0/478.0 [MH+].

Example 30

3-{4-[3-(Dimethylamino)propoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile trifluoroacetate

The title compound (34 mg, 60%) was synthesized from 4-(5-cyano-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (32 mg, 0.10 mmol) and *N*-(3-chloropropyl)-*N*,*N*-dimethylamine hydrochloride (18 mg, 0.11 mmol).
^{1}H-NMR (CD_3OD): δ 8.55 (2H, d); 8.19 (1H, d); 7.47-7.53 (2H, m); 7.33-7.38 (3H, m); 7.30 (2H, d); 7.10 (2H, d); 4.27 (2H, dd); 3.73 (2H, dd); 2.96 (6H, s); 2.25 (2H, dddd).
APCI-MS m/z: 397.2 [MH+].

Example 31

5-{[4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]methyl}-1,3-oxazolidin-2-one trifluoroacetate

The title compound (14 mg, 11%) was synthesized from 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (98 mg, 0.27 mmol) and 5-(chloromethyl)-1,3-oxazolidin-2-one (38 mg, 0.28 mmol).
^{1}H-NMR (CD_3OD): δ 8.27 (1H, d); 8.18 (1H, d); 7.47-7.53 (2H, m); 7.31-7.40 (3H, m); 6.88-6.99 (4H, m); 4.89-4.97 (1H, m); 4.08 (2H, ddd); 3.69 (1H, dd); 3.50 (1H, dd).
APCI-MS m/z: 365.0/367.0 [MH+].

Example 32

3-{4-[3-(dimethylamino)propoxy]phenyl}-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile trifluoroacetate

The title compound (23 mg, 33%) was synthesized from 3-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (45 mg, 0.13 mmol) and *N*-(3-chloropropyl)-*N*,*N*-dimethylamine hydrochloride (23 mg, 0.15 mmol).
APCI-MS m/z: 427.2 [MH+].

Example 33

(3-{4-[5-Bromo-2-(4-methoxy-phenyl)-1*H*-pyrrolo[1,3-*b*]pyridin-3-yl]-phenoxy}-propyl)-dimethylamine

a) 4-[5-Bromo-2-(4-methoxy-phenyl)-1-*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-phenol

(4-Bromo-2-phenyl)-hydrazine (0.5 g, 2.66 mmol) and 2-(4-hydroxy-phenyl)-1-(4-methoxy-phenyl)-ethanone (0.644g, 2.66 mmol) in benzene (20 mL) containing acetic acid (0.2 mL) was heated at reflux temperature. Water was continuously distilled off using a Dean-Stark trap. After 13h, the reaction mixture was cooled and triethylamine (0.4 mL) was added. The mixture was evaporated and the residue was re-suspended in water. The precipitate was filtered off to give 4-[2-[(4-bromophenyl)-hydrazono]-2-(4-methoxy-phenyl)-ethyl]-phenol (0.93 g, 84%).
^{1}H-NMR (DMSO-d_6): δ 10.06 (1H, s), 9.20 (1H, s), 8.18 (1H, d), 7.82 (1H, dd), 7.75 (2H, d), 7.30 (1H, d), 6.97 (2H, d), 6.91 (2H, d), 6.65 (2H, d), 4.16 (2H, s); 3.73 (3H, s).
APCI-MS m/z: 411.9; 413.9 [MH+].

4-[2-[(4-Bromophenyl)-hydrazono]-2-(4-methoxy-phenyl)-ethyl]-phenol (708 mg, 1.72 mmol) was stirred in an inert atmosphere at 230 °C for 10 minutes. The crude product was purified by column chromatography (silica gel, ethyl acetate-heptane 2:3) and crystallized twice from methanol to give the title compound (23 mg, 3%).

^{1}H-NMR (DMSO-d_6): δ 12.17 (1H, bs), 9.46 (1H, bs), 8.27 (1H, d), 7.87 (1H, d), 7.44 (2H, d), 7.13 (2H, d), 6.94 (2H, d), 6.81 (2H, d); 3.77 (3H, s).
APCI-MS m/z: 395.0/397.0 [MH+].

b) (3-{4-[5-Bromo-2-(4-methoxy-phenyl)-1*H*-pyrrolo[1,3-*b*]pyridin-3-yl]-phenoxy}-propyl)-dimethylamine

The title compound (13 mg, 16 %) was synthesized from crude 4-[5-bromo-2-(4-methoxy-phenyl)-1-*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-phenol (75 mg, purity 87%, 0.14 mmol) and *N*-(3-chloropropyl)-*N*,*N*-dimethylamine hydrochloride.

^{1}H-NMR (DMSO-d_6): δ 12.22 (1H, bs), 8.28 (1H, d), 7.88 (1H, d), 7.43 (1H, d), 7.23 (1H, d), 6.96 (1H, d), 6.95 (1H, d), 4.02 (2H, t), 3.77 (3H, s), 2.37 (2H, t), 2.15 (6H, s) and 1.86 (2H, p).
APCI-MS m/z: 480.2; 482.1 [MH+].

Example 34

3-[4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]propan-1-amine trifluoroacetate

A mixture of 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (83 mg, 0.23 mmol), sodium hydride (60% suspension in mineral oil, 22 mg, 0.55 mmol) and N,N-dimethylformamide (2 ml) was heated at 60 °C for 30 minutes. A solution of 2-(3-chloropropyl)-1*H*-isoindole-1,3(2*H*)-dione (61 mg, 0.23 mmol) in N,N-dimethylformamide (500 µl) was added and the reaction mixture was further stirred at 60 °C for 6h. Water (1 ml) tetrahydrofuran (10 ml), methanol (10 ml) and 2M ethylamine solution in ethanol (4 ml) were added and the reaction mixture was stirred at room temperature for 14h. The solvents were evaporated off and the residue was dissolved in 1,4-dioxane (10 ml) and water (5 ml) containing sodium hydroxide (4.56 g, 0.11 mol) and the reaction mixture was heated at 100 °C for 2 h. After cooling, the product was extracted into ethyl acetate and purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient 10:90:0.1 to 95:5:0.1) to give the title compound (4 mg, 3%).

^{1}H-NMR (CD_3OD): δ 8.27 (1H, d); 7.96 (1H, d); 7.45-7.53 (3H, m); 7.31-7.38 (2H, d); 7.27 (2H, d); 7.08 (2H, d); 4.17 (2H, dd); 3.19 (2H, dd); 2.14-2.22 (2H, ddd).
APCI-MS m/z: 421.9/423.9 [MH+].

Example 35

5-Bromo-3-(4-aminomethylphenyl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine

To 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (1.00 g, 2.7 mmol) and tetrahydrofuran (5 ml) was added lithium aluminium hydride (1M solution in diethyl ether, 5.7 ml, 5.7 mmol) during 4h. The reaction mixture was stirred at room temperature for a further 30 minutes and then neutralized by adding methanol and dilute hydrochloric acid. The crude product was purified by column chromatography (silica gel, ethyl acetate/chloroform/methanol/aqueous ammonia gradient 100:0:0:0, 0:95:5:0 and 0:80:19.5:0.5) to give the title compound (0.569 g, 56%).
^{1}H-NMR (CD_3OD): δ 8.43 (1H, d); 8.23 (1H, d); 7.34-7.55 (9H, m) 4.17 (2H, s).
APCI-MS m/z: 377.0/379.0 [MH+].

Example 36

5-Bromo-3-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine trifluoroacetate.

A mixture of 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (82 mg, 0.22 mmol), 1,2-ethanediamine (41 mg, 0.68 mmol), 4-methylbenzenesulfonic acid hydrate (89 mg, 0.47 mmol), glycol (0.3 ml) and DMSO (0.4 ml) was heated at 175 °C for 3h. After cooling, methanol (1 ml) was added and the product was purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the title compound (11 mg, 9%).
^{1}H-NMR (CD_3OD): δ 8.34 (1H, d); 8.14 (1H, d); 7.86 (2H, d); 7.61 (2H, d); 7.46-7.50 (2H, m); 7.36-7.43 (3H, m); 4.22 (4H, s).

APCI-MS m/z: 417.1/419.1 [MH+].

Example 37

5-Bromo-3-[4-(4,4-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine trifluoroacetate

The title compound (5 mg, 4%) was synthesized from 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (82 mg, 0.22 mmol) and 2-methylpropane-1,2-diamine (27 mg, 0.31 mmol) essentially as described in Example 36.
^{1}H-NMR (CD_3OD): δ 8.35 (1H, d); 8.14 (1H, d); 7.85 (2H, d); 7.62 (2H, d); 7.46-7.49 (2H, m); 7.38-7.42 (3H, m); 3.87 (2H, s); 3.35 (2H, s); 1.57 (6H, s).
APCI-MS m/z: 445.0/447.0 [MH+].

Example 38

N-(2-Aminoethyl)-4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide trifluoroacetate

The title compound (10 mg, 8%) was isolated from the synthesis of 5-bromo-3-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine trifluoroacetate (Example 36).
^{1}H-NMR (CD_3OD): δ 8.31 (1H, d); 8.07 (1H, d); 7.90 (2H, d); 7.44-7.51 (4H, m); 7.37-7.40 (3H, m); 3.69 (2H, dd); 3.18 (2H, dd).
APCI-MS m/z: 435.1/437.0 [MH+].

Example 39

3-[[4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzyl](1,2-dihydroxypropyl)amino]propane-1,2-diol trifluoroacetate

To 1-[4-(5-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)phenyl]methanamine (58.5 mg, 0.15 mmol) and tetrahydrofuran (5 ml) was added oxiran-2-ylmethanol (77 mg, 5.7 mmol) in three batches during 4h at 80 °C. Methanol (1 ml) was added and the product was purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the title compound (32 mg, 32%).

^{1}H-NMR (CD_3OD): δ 8.26 (1H, d); 8.03 (1H, d); 7.40-7.60 (6H, m); 7.30-7.36 (3H, m); 3.88-4.20 (2H, m); 3.48-3.64 (4H, m); 3.20-3.45 (4H, m).

APCI-MS m/z: 526.1/528.1 [MH+].

Example 40

4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid

A solution of 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile (135 mg, 0.36 mmol), conc. sulphuric acid (2 ml), water (2 ml) and 1,4-dioxane (2 ml) was heated at 120 °C for 2h. After cooling, water (100 ml) was added and the precipitate was purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the title compound (33 mg, 23%).

^{1}H-NMR (CD_3OD): δ 8.60 (1H, d); 8.05 (1H, d); 7.35-7.54 (9H, m).

APCI-MS m/z: 393.0/395.0 [MH+].

Example 41

N^5-[4-(5-Bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzyl]glutamine trifluoroacetate

A mixture of Boc-Glu-OtBu (53 mg, 0.18mmol), HATU (72 mg, 0.19 mmol) and dichloromethane (2 ml) was adjusted to pH 8 with diisopropylethyl amine. After 20 minutes a solution of 1-[4-(5-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)phenyl]methanamine (65 mg, 0.17 mmol) in NMP (1 ml) was added and the pH was adjusted to 8 with diisopropylethyl amine. After 6h, trifluoroacetic acid (1.5 ml) was added. After 17h, the solvents were evaporated off and the crude product was purified by

preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the title compound (41 mg, 38%).

^{1}H-NMR (CD_3OD): δ 8.40 (1H, d); 8.05 (1H, d); 7.37-7.61 (9H, m); 4.17 (2H, dd); 2.26-2.60 (4H, m).

APCI-MS m/z: 507.0/509.0 [MH+].

Example 42

3-(4-Hydroxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile

A mixture of 4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol (355 mg, 0.97 mmol), zinc cyanide (137 mg, 1.17 mmol), tris(dibenzylideneacetone)dipalladium(0) (89 mg, 97 μmol), bis(diphenylphosphine)ferrocene (129 mg, 0.23 mmol) and N,N-dimethylformamide (10 ml) was stirred at 130 °C for 20h. Ethyl acetate (100 ml) was added and the organic phase was washed with water (2 x 50 ml), dried and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, ethyl acetate/heptane gradient from 3:7 to 8:2) and crystallization (6 ml tetrahydrofuran/heptane 5:1) to give the title compound (115 mg, 38%).

^{1}H-NMR (DMSO-d6): δ 12.65 (1H, s); 9.50 (1H, s); 8.62 (1H, d); 8.26 (1H, d); 7.50 (2H, dd); 7.32-7.43 (3H, m); 7.15 (2H, d); 6.79 (2H, d).

APCI-MS m/z: 312.1 [MH+].

Following the general method of Example 42, the compounds of Examples 43 to 45 were prepared:

Example 43

3-[4-(Aminomethyl)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile trifluoroacetate

The title compound (12 mg, 10%) was synthesized from 1-[4-(5-bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)phenyl]methanamine (104 mg, 0.27 mmol) and purified by

preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1).

^{1}H-NMR (CD_3OD): δ 8.58 (1H, d); 8.24 (1H, d); 7.45-7.53 (6H, m); 7.32-7.40 (3H, m); 4.18 (2H, s)

APCI-MS m/z: 325.4 [MH+, weak], 308.1 [MH+ -NH_3].

Example 44

3-(4-Morpholin-4-ylphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile

The title compound (5 mg, 11%) was synthesized from 5-bromo-3-(4-morpholin-4-ylphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (50 mg, 0.115 mmol).

^{1}H-NMR (DMSO-d6): δ 12.61 (1H, s); 8.58 (1H, d); 8.21 (1H, d); 7.28-7.44 (7H, m); 6.93 (2H, d); 3.71 (4H, dd); 3.16 (4H, dd).

APCI-MS m/z: 381.2 [MH+].

Example 45

3-(4-Hydroxyphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile

The title compound (50 mg, 93%) was synthesized from 4-[5-bromo-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]phenol (62 mg, 0.16 mmol).

^{1}H-NMR (DMSO-d6): δ 12.59 (1H, s); 9.48 (1H, s); 8.48 (1H, d); 8.20 (1H, d); 7.44 (2H, d); 7.15 (2H, d); 6.95 (2H, d); 6.80 (2H, d).

APCI-MS m/z: 342.1 [MH+].

Example 46

5-Bromo-2-(4-methoxy-phenyl)-3-piperazin-1-yl-1H-pyrrolo[2,3-b]pyridine trifluoroacetate

4-[5-Bromo-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester bis TFA salt (6 mg, 0.0084 mmol) was dissolved in dichloromethane (5 ml) and TFA (1 ml) was added. The mixture was heated to reflux for 30 minutes and then concentrated in vacuo. The residue was recrystallized from ethyl acetate to give the pure title compound as a mono-TFA salt, white powder (2 mg, 48%).

^{1}H-NMR (acetone-d_6): δ 12.00 (1H, s); 8.58 (2H, bs); 8.24 (2H, s); 8.01 (2H, d); 7.04 (2H, d); 3.81 (3H, s); 3.35-3.20 (8H, m).

APCI-MS m/z: 387.0 [MH+].

Example 47

5-Bromo-2-(4-methoxyphenyl)-3-(4-methylpiperazin-1-yl)-1H-pyrrolo[2,3-b]pyridine

2-Bromo-1-(4-methoxyphenyl)-ethanone (1.14 g, 5 mmol) was dissolved in N,N-dimethylformamide (20 ml). 1-Methylpiperazine (1.04 g, 10 mmol) was added and after 10 minutes the reaction mixture was diluted with water (200 ml) and the mixture extracted with ethyl acetate (3 x 200 ml). The combined organic phase was washed with brine (2 x 20 ml) and dried ($MgSO_4$) and the solvents evaporated. This afforded the crude piperazinomethylketone as a pale yellow oil that solidified upon standing (540 mg, 43 %) which was used in the next step without further purification. This ketone (248 mg, 1 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (188 mg, 1 mmol) were heated together at 230 °C for 1h. When cool, the dark brown glassy solid was dissolved in N,N-dimethylformamide (2 ml) and subjected to preparative HPLC. This afforded a crude product (27 mg, 7%) that was approximately 90% pure. This material was purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give pure (>99%) product as a white powder (5 mg).

^{1}H-NMR (DMSO-d_6): δ 12.01 (1H, s); 9.60 (1H, bs); 8.24 (2H, m); 8.02 (2H, d); 7.03 (2H, d); 3.81 (3H, s); 3.58-3.45 (4H, m); 3.55-3.20 (4H, m); 2.91 (3H, s).

APCI-MS m/z: 401.0 [MH+].

Example 48

4-[5-Bromo-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester bis-trifluoroacetate

2-Bromo-1-(4-methoxyphenyl)-ethanone (1.14 g, 5 mmol) was dissolved in N,N-dimethylformamide (20 ml). 1-Piperazine-1-carboxylic acid tert-butyl ester (931 mg, 5 mmol) and DIEA (0.85 ml, 5 mmol) were added and after 10 minutes the reaction mixture was diluted with water (200 ml) and the mixture extracted with ethyl acetate (3 x 200 ml). The combined organic phase was washed with brine (2 x 20 ml) and dried ($MgSO_4$) and the solvents evaporated. This afforded the crude protected piperazinomethylketone as a pale yellow oil that solidified upon standing (1.65 g, 99%) which was used in the next step without further purification. This ketone (334 mg, 1 mmol) and (5-bromo-pyridin-2-yl)-hydrazine (188 mg, 1 mmol) were heated together for 30 minutes at 110 °C and then at 200 °C for 45 minutes. The crude product was purified twice by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the pure (>99%) product as a white powder (12 mg, 2.5%). ^{1}H-NMR (acetone-d_6): δ 10.78 (1H, s); 8.24(1H, s); 8.16 (1H, s); 8.10 (2H, d); 7.03 (2H, d); 3.84 (3H, s); 3.57 (4H, t); 3.18 (4H, t); 2.93 (1.8 H, bs); 1.46 (9H, s). APCI-MS m/z: 487.2 [MH+].

Example 49

5-Bromo-2-(4-methoxyphenyl)-3-morpholin-4-yl-1H-pyrrolo[2,3-*b*]pyridine

2-Bromo-1-(4-methoxyphenyl)-ethanone (5 g, 25 mmol) was dissolved in N,N-dimethylformamide (15 ml). Morpholine (4.35 g, 50 mmol) was added and the solution turned yellow and became warm. As it was allowed to cool, morpholine hydrobromide crystallized out and was removed by filtration. The filtrate was diluted with toluene (100 ml) and (5-bromo-pyridin-2-yl)-hydrazine (4.7 g, 25 mmol) was added. The resulting mixture was refluxed for 14h, while azeotropically removing water. The solvents

were removed in vacuo and the resulting red-brownish oil was purified by column chromatography (silica gel, ethyl acetate/heptane gradient 0:100 to 100:0). The second eluting component was collected and concentrated in vacuo to give the hydrazone as a brown oil (6.8 g, 72%). This oil (1.07 g, 2.8 mmol) was heated to 200-205 °C for 40 minutes and then allowed to cool. The dark brown glassy product was dissolved in boiling acetonitrile and the title compound crystallised as this solution was allowed to cool. The product was collected by filtration and thoroughly washed with acetonitrile. This crude product was further recrystallized from acetone/dichloromethane to afford a pale yellow powder (8 mg, 0.80%).

^{1}H-NMR (DMSO-d_6): δ 11.99 (1H, bs); 8.35 (1H, s); 8.24 (1H, s); 8.12 (2H, d); 7.48 (2H, t); 7.35 (1H, t); 3.73 (4H, t); 3.13 (4H, t).

APCI-MS m/z: 358.2 [MH+].

Example 50

5-Bromo-3-(4-methanesulfonylpiperazin-1-yl)-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine

Piperazine-1-carboxylic acid tert-butyl ester (1.86 g, 10 mmol) was dissolved in pyridine (15 ml) and methanesulfonyl chloride (1.14 g, 10 mmol) was added. The mixture turned yellow and become warm. After 10 minutes, the reaction was diluted with water (150 ml) and left standing, whereupon the precipitate was collected. To this precipitate, dichloromethane (15 ml) and trifluoroacetic acid (2.5 ml) were added. The mixture was heated to boiling and then left to cool. The solvent was removed and the resulting yellow oil was dissolved in ethyl acetate (20 ml). Crystals of 1-(methylsulfonyl)piperazine trifluoroacetate were collected by filtration (0.871 g, 72%). 1-(Methylsulfonyl)piperazine trifluoroacetate was dissolved in N,N-dimethylformamide (5 ml) and *N*-ethyl-*N*,*N*-diisopropylamine (2.2 ml, 13 mmol) was added, followed by 2-bromo-1-(4-methoxyphenyl)-ethanone (0.72 g, 3.1 mmol). After 5 minutes, the reaction mixture was poured into water (50 ml) and crystals of 2-(4-methanesulfonyl-piperazin-1-yl)-1-(4-methoxy-phenyl)-ethanone were collected (1.11 g, 67%). Part of this ketone (312 mg, 1 mmol) and (5-bromopyridin-2-yl)-hydrazine (188 mg, 1 mmol) were fused together at 210

°C for 30 minutes. After cooling, the crude product was crystallized from acetonitrile to give the title compound (31 mg, 7%).

^{1}H-NMR (DMSO-d_6): δ 11.92 (1H, s); 8.31 (1H, s); 8.20 (1H, s); 8.04 (2H, d); 7.05 (2H, d); 3.81 (3H, s); 3.7-3.3 (8H, m); 2.97 (3H, s).

APCI-MS m/z: 465.4 [MH+].

Example 51

4-[5-Bromo-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-piperazine-1-carbaldehyde

2-Bromo-1-(4-methoxyphenyl)-ethanone (2.24 g, 10 mmol) was dissolved in N,N-dimethylformamide (20 ml). Piperazine-1-carbaldehyde (2.3 g, 20 mmol) and *N*-ethyl-*N*,*N*-diisopropylamine (0.85 ml, 5 mmol) were added and after 30 minutes the reaction mixture was diluted with ethyl acetate (100 ml) and the mixture washed with brine (4 x 100 ml). The organic phase was dried ($MgSO_4$) and the solvent evaporated off. The residue was dissolved in a mixture of toluene (50 ml) and (5-bromo-pyridin-2-yl)-hydrazine (1.88 g, 10 mmol). The mixture was heated at reflux for 4h and then allowed to cool. The solvent was removed in vacuo and the residue chromatographed (silica gel, ethyl acetate/heptane 1:1). Crude 4-[2-[(5-bromopyridin-2-yl)hydrazono]-2-(4-methoxyphenyl)ethyl]piperazine-1-carbaldehyde was heated at 210 °C for 20 minutes. The crude product was purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1). Appropriate fractions were evaporated and the solid was washed with a 1:1 acetonitrile/water mixture to give the title compound (12 mg, 0.3%).

^{1}H-NMR (DMSO-d_6): δ 11.90 (1H, s); 8.32 (1H, s); 8.19 (1H, s); 8.09 (2H, d); 8.08 (1H, s); 7.05 (2H, d); 3.80 (3H, s); 3.54 (2H, t); 3.50 (2H, t); 3.15 (2H, t); 3.06 (3H, t).

^{13}C-NMR (DMSO-d_6): δ 160.8; 158.8; 144.8; 142.0; 131.8; 128.8; 128.7; 123.3; 122.2; 118.7; 113.8; 110.2; 55.1; 52.4; 51.4; 45.7; 40.1.

APCI-MS m/z: 415.3 [MH+].

Example 52

5-Bromo-2-phenyl-3-pyrrol-1-yl-1H-pyrrolo[2,3-b]pyridine

5-Bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-ylamine (60 mg, 0.2 mmol) was suspended in acetic acid (20 ml) and 2,5-dimethoxytetrahydrofuran (0.030 ml, 0.22 mmol) added. The mixture was refluxed for 1.5h, cooled and concentrated in vacuo. The residue was chromatographed (silica gel, heptane/ethyl acetate gradient from 1:0 to 0:1). This gave the product as an off-white powder (59.1 mg, 84%). An analytical sample was further purified by recrystallisation from acetonitrile/toluene/ethyl acetate.

^{1}H-NMR (DMSO-d_6): δ 12.59 (1H, bs); 8.37 (1H, s); 7.80 (1H, s); 7.40-7.25 (5H, m); 6.86 (2H, t); 6.29 (2H, t).

APCI-MS m/z: 338.0/340.0 [MH+].

Example 53

5-Cyano-2-(4-methoxy-phenyl)-3-pyrrol-1-yl-1H-pyrrolo[2,3-b]pyridine

The title compound (25 mg, 16%) was synthesized from 6-hydrazino-nicotinonitrile (70 mg, 0.5 mmol), and 1-(4-methoxyphenyl)-2-(1H-pyrrol-1-yl)ethanone (110 mg, 0.5 mmol) essentially as described for Example 1 and purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1).

^{1}H-NMR ($CDCl_3$): δ 11.18 (1H, bs); 8.53 (1H, s); 8.17 (1H, s); 7.25 (2H, d); 6.94 (2H; d); 6.76 (2H, t); 6.41 (2H, t); 3.84 (3H, s).

APCI-MS m/z: 315.1 [MH+].

Example 54

5-Bromo-3-(2,5-dimethyl-pyrrol-1-yl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine

5-Bromo-2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-ylamine (48 mg, 0.16 mmol) was suspended in acetic acid (20 ml) and hexane-2,5-dione (0.025 ml, 0.20 mmol) added. The mixture was refluxed for 1.5h and then concentrated *in vacuo*. The crude product was purified by preparative HPLC (RP-18, acetonitrile/water/trifluoroacetic acid gradient from 10:90:0.1 to 95:5:0.1) to give the title compound (17 mg, 29%).

^{1}H-NMR (DMSO-d_6): δ 11.55 (1H, bs); 8.36 (1H, s); 7.77 (1H, s); 7.39-7.31 (5H, m); 5.93 (2H, s); 1.86 (6H, s).

APCI-MS m/z: 366.3/368.3 [MH+].

Screen

Itk LANCE TRF assay

The Itk kinase assay utilized recombinant human Itk kinase domain fused with GST (Glutathione S-Transferase). The protein was expressed in High five insect cells, purified in one step on an affinity chromatography glutathione column and stored in 50 mM Tris/HCl (pH 7.6), 150 mM NaCl, 5% (w/v) mannitol, 1 mM DTT, 30% glycerol at –70 °C. The kinase substrate used in the assay was a biotinylated peptide derived from the Src-optimal substrate (Nair *et al*, J. Med. Chem., 38: 4276, 1995; biotin-AEEEIYGEFEAKKKK).

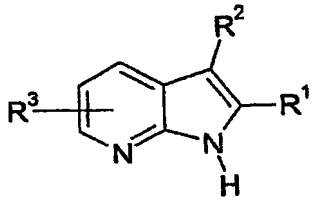
The assay additions were as follows: Test compounds (or controls; 1 µL in 100% DMSO) were added to black 96-well flat-bottomed plates (Greiner 655076) followed by 20 µL Itk in assay buffer and the reaction was started by adding 20 µL ATP and peptide substrate in assay buffer. The assay buffer constitution during phosphorylation was: 50 mM HEPES (pH 6.8), 10 mM $MgCl_2$, 0.015% Brij 35, 1 mM DTT, 10% glycerol, 160 ng/well Itk, 2 µM peptide substrate and 50 µM ATP. The assay was stopped after 50 minutes (RT) by adding 150 µL ice-cold Stop solution (50 mM Tris/HCl, pH 7.5, 10 mM EDTA, 0.9% NaCl and 0.1% BSA) together with LANCE reagents (2 nM PT66-Eu^{3+}, Wallac AD0069 and 5 µg/ml Streptavidin-APC, Wallac AD0059. Both concentrations were final in stopped

assay solution). The plates were measured on a Wallac 1420 Victor 2 instrument with TRF settings after 1h incubation, and the ratio (665 signal/615 signal)*10000 was used to calculate the inhibition values. IC_{50} values were determined using XLfit.

When tested in the above screens, the compounds of Examples 1 to 54 gave IC_{50} values for inhibition of Itk activity of less than 25 μM, indicating that the compounds of the invention are expected to possess useful therapeutic properties.

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms selected independently from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy or CO_2R^4;

R^2 represents a saturated or partially unsaturated 4 to 7 membered ring, optionally including 1 or 2 heteroatoms independently selected from O, N and $S(O)_n$ and optionally incorporating 1 or 2 carbonyl groups; and optionally substituted by halogen, OH, C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkanoyl, C1 to 4 alkylsulphonyl or CO_2R^5;

or R^2 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CN, CO_2R^6 and a group –W-X-Y;

W represents O or a bond;

X represents C1 to 4 alkyl, -CO-, $-CH_2CHOHCH_2-$ or a bond;

Y represents NR^7R^8;

or Y represents a saturated or partially unsaturated 4 to 7 membered ring, optionally including 1 or 2 heteroatoms independently selected from O, N and $S(O)_n$ and optionally incorporating 1 or 2 carbonyl groups; and optionally substituted by one or more substituents selected independently from OH, C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkanoyl, C1 to 4 alkylsulphonyl or CO_2R^5;

or Y represents C1 to 4 alkoxy optionally further substituted by OH or C1 to 4 alkoxy;

R^3 represents H, halogen, C1 to 4 alkyl, C1 to 4 alkoxy or cyano;

R^4, R^5 and R^6 independently represent H or C1 to 4 alkyl;

R^7 and R^8 independently represent H, C1 to 4 alkyl, $-CH_2CHOHCH_2OH$, C1 to 4 alkanoyl or a group –G–J–K wherein G represents –CO– or a bond; J represents C1 to 4 alkyl; and K represents $-NR^9R^{10}$ or $-CH(NH_2)CO_2R^{11}$;

R^9 and R^{10} independently represent H or C1 to 4 alkyl; or the group $-NR^9R^{10}$ together represents a saturated 5 or 6 membered azacyclic ring;

R^{11} represents H or C1 to 4 alkyl;

n represents an integer 0, 1 or 2;

and pharmaceutically acceptable salts thereof;
provided that:

(i) when R^3 is at the 6-position and represents C1 to 4 alkoxy and at the same time R^1 represents optionally substituted phenyl, then R^2 does not represent unsubstituted 4-pyridyl or unsubstituted 4-pyrimidyl; and

(ii) when R^2 represents 4-hydroxyphenyl or 4-hydroxy-3-pyridyl either optionally further substituted by halogen, C1 to 4 alkyl or C1 to 4 alkoxy, then R^3 represents cyano; and

(iii) the following three compounds are disclaimed - 2-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrrolo[2,3-b]pyridine; 2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine; and 4-methyl-2,3-diphenyl-1H-pyrrolo[2,3-b]pyridine.

2. A compound according to Claim 1 wherein R^3 represents halogen or cyano.

3. A compound according to Claim 1 or Claim 2 wherein W represents O.

4. A compound of formula (I), according to any one of Claims 1 to 3, which is:

5-bromo-3-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;
5-bromo-3-(3-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;
4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzonitrile;
5-bromo-2-(2-furyl)-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;
3-{4-[5-bromo-2-(2-furyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]phenoxy}-*N*,*N*-dimethylpropan-1-amine;
5-bromo-3-(4-morpholin-4-ylphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;
5-bromo-2,3-diphenyl-1*H*-pyrrolo[2,3-*b*]pyridine;
5-bromo-2-(4-bromophenyl)-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;
5-bromo-2,3-bis(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine;
N-(3-{4-[5-bromo-2-(2-furyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]phenoxy}propyl)-*N*,*N*-dimethylamine;
5-bromo-3-phenyl-2-(1,3-thiazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine;
5-bromo-3-furan-2-yl-1-*H*-pyrrolo[2,3-*b*]pyridine;

N-[5-(5-bromo-2-phenyl-1-*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-fuan-2-ylmethyl]-acetamide;

5-bromo-3-(5-aminomethylfuran-2-yl)-2-phenyl-1H-pyrrolo[2,3-*b*]pyridine;

5-bromo-2,3-difuran-2-yl-1*H*-pyrrolo[2,3-*b*]pyridine;

methyl 5-(5-bromo-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1*H*-pyrrole-2-carboxylate;

5-bromo-3-phenyl-2-(1H-pyrrol-3-yl)-1H-pyrrolo[2,3-b]pyridine;

5-bromo-3-phenyl-2-(1,3-oxazol-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine;

3-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenol;

1-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-3-[(2-pyrrolidin-1-ylethyl)amino]propan-2-ol;

1-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-3-pyrrolidin-1-ylpropan-2-ol;

5-bromo-3-{4-[2-(1-methylpyrrolidin-2-yl)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-2-phenyl-3-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-[4-(2-morpholin-4-ylethoxy)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-[3-(2-morpholin-4-ylethoxy)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

3-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]-*N*,*N*-dimethylpropan-1-amine;

5-bromo-3-{4-[2-(2-methoxyethoxy)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-{3-[2-(1-methylpyrrolidin-2-yl)ethoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

3-{4-[3-(dimethylamino)propoxy]phenyl}-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

5-{[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]methyl}-1,3-oxazolidin-2-one;

3-{4-[3-(dimethylamino)propoxy]phenyl}-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

(3-{4-[5-bromo-2-(4-methoxy-phenyl)-1*H*-pyrrolo[1,3-*b*]pyridin-3-yl]-phenoxy}-propyl)-dimethylamine;

3-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)phenoxy]propan-1-amine;

5-bromo-3-(4-aminomethylphenyl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine;

5-bromo-3-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-2-phenyl-1H-pyrrolo[2,3-b]pyridine;

5-bromo-3-[4-(4,4-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine;

N-(2-aminoethyl)-4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzamide;

3-[[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzyl](1,2-dihydroxypropyl)amino]propane-1,2-diol;

4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzoic acid;

N^5-[4-(5-bromo-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzyl]glutamine;

3-(4-hydroxyphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

3-[4-(aminomethyl)phenyl]-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

3-(4-morpholin-4-ylphenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

3-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile;

5-bromo-2-(4-methoxy-phenyl)-3-piperazin-1-yl-1H-pyrrolo[2,3-b]pyridine;

5-bromo-2-(4-methoxyphenyl)-3-(4-methylpiperazin-1-yl)-1H-pyrrolo[2,3-b]pyridine;

4-[5-bromo-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-piperazine-1-carboxylic acid tert-butyl ester;

5-bromo-2-(4-methoxyphenyl)-3-morpholin-4-yl-1H-pyrrolo[2,3-*b*]pyridine;

5-bromo-3-(4-methanesulfonylpiperazin-1-yl)-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridine;

4-[5-bromo-2-(4-methoxy-phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-piperazine-1-carbaldehyde;

5-bromo-2-phenyl-3-pyrrol-1-yl-1H-pyrrolo[2,3-b]pyridine;

5-cyano-2-(4-methoxy-phenyl)-3-pyrrol-1-yl-1H-pyrrolo[2,3-b]pyridine;

5-bromo-3-(2,5-dimethyl-pyrrol-1-yl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine;

3-(4-methoxyphenyl)-2-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile;

or a pharmaceutically acceptable salt of any one thereof.

5. A compound of formula (I), according to Claim 1, or a pharmaceutically acceptable salt thereof, for use as a medicament.

6. A pharmaceutical formulation comprising a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, optionally in admixture with a pharmaceutically acceptable diluent or carrier.

7. A method of treating, or reducing the risk of, a human disease or condition in which inhibition of Itk kinase activity is beneficial which comprises administering to a person suffering from or susceptible to such a disease or condition, a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof.

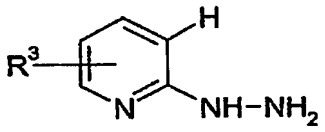
8. The use of a compound of formula (I) as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of Itk kinase activity is beneficial.

9. The use according to Claim 8 wherein the disease is asthma.

10. The use according to Claim 8 wherein the disease is allergic rhinitis.

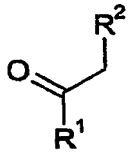
11. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 4, and optical isomers and racemates thereof and pharmaceutically acceptable salts thereof, which comprises:

reaction of a compound of formula (II):



(II)

in which R^3 is as defined in Claim 1, with a compound of formula (III):



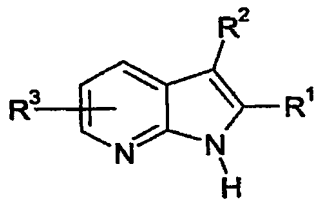
(III)

in which R^1 and R^2 are as defined in Claim 1;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

Abstract

There are provided novel compounds of formula (I)



(I)

wherein R^1, R^2 and R^3 are as defined in the specification and pharmaceutically acceptable salts thereof; together with processes for their preparation, compositions containing them and their use in therapy. The compounds are inhibitors of the kinase Itk.